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10/564,609	01/12/2006	Dmitry Dmitrievich Genkin	06-1663	8872

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,609	GENKIN ET AL.	
	Examiner	Art Unit	
	DELIA M. RAMIREZ	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-4 are pending.

Applicant's election of Group 2, claims 1-4, drawn in part to a method of treating fungal infections wherein said method requires administration of a DNA-destroying agent into systemic blood as submitted in a communication filed on 4/17/2009 is acknowledged. It is noted that applicant's reference to Group I as the group encompassing the elected invention has been interpreted as a typographical error since the elected subject matter (treatment of fungal infections) is that of Group 2, as set forth in the restriction requirement mailed on 3/19/2009.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-4 as they relate to a method of treating fungal infections by administration of a DNA destroying agent in systemic blood circulation are being examined herein.

Specification

1. The specification is objected to for the following reasons: (a) the term "Albicans" should be amended to recite "albicans" (5 instances), (b) the term "Candida Albicans [unknown character] St. Aureus" on page 10, lines 16-17 should be amended to recite "*Candida albicans* and *S. aureus*", (c) the term "DNAase" should be amended to recite "DNase" (page 7, line 17), and (d) the term "Brief Description of the Drawings" should be deleted because there are no drawings to describe in the specification. Appropriate correction is required.

2. The abstract of the specification is objected to for failing to comply with the proper language and/or format as set forth in MPEP § 608.01(b). The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that

the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc. Appropriate correction is required.

Priority

3. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to RUSSIAN FEDERATION PCT/RU03/00304 filed on 07/14/2003, and RUSSIAN FEDERATION 2004108057 filed on 03/12/2004. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

4. This application is the US national stage of PCT/RU04/00260 filed on 07/01/2004.

Claim Objections

5. Claim 1 is objected to due to the recitation of "characterized by introducing of….agent into a systemic blood circulation". The term should be amended to recite "wherein said method comprises introducing a blood…destroying agent into the systemic blood circulation". Appropriate correction is required.

6. Claims 2-4 are is objected to due to the recitation of "DNAase". This term should be replaced with "DNase". Appropriate correction is required.

7. Claim 2 is objected to due to the recitation of "wherein DNAase enzyme is introduced into a systemic blood circulation". The term should be replaced with "wherein the blood extracellular DNA destroying agent is a DNase". Appropriate correction is required.

8. Claim 3 is objected to due to the recitation of "which characterized by….to provide blood extracellular….which can be revealed by pulse- gelelectrophoresis". The term should be replaced with "wherein the blood extracellular DNA destroying agent is a DNase which is introduced in doses sufficient to provide a blood extracelullar….change as revealed by pulse-field gel electrophoresis". Appropriate correction is required.

9. Claim 4 is objected to due to the recitation of "characterized by introducing of DNAase enzyme in doses and regimens which provide blood plasma DNA-hydrolytic activity , measured in blood plasma, to exceed 150 Kunitz units per liter of plasma during more then 12 hours in total within 24 hours". The term should be replaced with "wherein the blood extracellular DNA destroying agent is a DNase which is introduced in a dose and regime that results in a DNA hydrolytic activity in blood plasma that exceeds 150 Kunitz units per liter of blood plasma for more than 12 hours within a period of 24 hours.". Appropriate correction is required.

10. Claims 1-4 are objected to as being directed to non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claim 1 (claims 2-4 dependent thereon) is indefinite in the recitation of "in particular: generalized infectious diseases caused by bacteria, diseases caused by fungi and protozoa, ….." because the presence of the term "in particular" prior to the list of diseases makes it unclear if the claimed method is limited only to the diseases listed after the term "in particular", or if additional diseases may be encompassed by

the claims. For examination purposes, it will be assumed that the term "in particular" is not present. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is directed to a method for treating diseases associated with qualitative/quantitative changes in blood extracellular DNA, including treatment of a genus of fungal infections, wherein said method requires the administration of a genus of extracellular DNA destroying agents. Claims 2-4 are directed to the method of claim 1 wherein the genus of fungal infections is treated with DNase.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics,

sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

As stated in claim 1, there is no actual structural limitation with regard to the members of the genus of extracellular DNA destroying agents required by the claimed method. Furthermore, there is no limitation in claims 1-4 with regard to the types of fungal infections that can be treated by the claimed method. While the specification in the instant application discloses practicing the claimed method with a single DNA destroying agent, i.e., DNase, for the treatment of *C. albicans* infections, it provides no clue as to the structural elements required in any DNA destroying agent, or the structural features found in a DNase which are also found in any DNA destroying agent. The specification fails to describe any additional species by any relevant, identifying characteristics or properties other than by functionality (i.e., DNA destroying activity). In addition, there is no disclosure as whether the administration of any DNA destroying agent or even DNase would be useful in the treatment of any fungal infection.

Claim 1 encompasses a large genus of DNA destroying agents which is structurally unrelated. A sufficient written description of a genus of compounds may be achieved by a recitation of a representative number of compounds defined by their structure or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of the genus of agents recited in the claim, and there is no information as to a correlation between structure and function. Furthermore, the structure of a DNase can not be representative of the structure of any DNA destroying agent since a DNase is a protein and a DNA destroying agent can be any chemical compound which is able to degrade DNA. Therefore, one cannot reasonably conclude that a DNase is representative of the structure of all DNA destroying agents as recited.

Due to the fact that the specification only discloses a single species of the genus of agents, i.e. DNase, and a single species of the genus of fungal infections, i.e., *C. albicans*, that can be treated with DNase, and the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

16. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating *C. albicans* infections wherein said method requires the introduction of DNase in the systemic blood circulation, does not reasonably provide enablement for a method for treating any fungal infection, wherein said method requires the administration of any extracellular DNA destroying agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 1-4 are broadly drawn in part to a method for treating any fungal infection by administering either any DNA destroying agent or DNase. The enablement provided is not commensurate in scope with the claim due to the extremely large number of DNA destroying agents of unknown structure required by the claimed method, and/or the large number of fungal

infections encompassed by the claimed method for which treatment with DNase or any DNA destroying agent is unknown. In the instant case, the specification enables a method for treating *C. albicans* infections wherein said method requires the introduction of DNase in the systemic blood circulation.

The amount of direction or guidance presented and the existence of working examples. The specification discloses a method for treating *C. albicans* infections in mice wherein said method requires intraperitoneal administration of DNase. However, the specification fails to provide any information as to the structural elements required in any compound that has DNA destroying activity or whether one could treat any fungal infection by administering any DNA destroying agent or DNase. No correlation between structure and the ability to destroy DNA has been provided.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. While the art discloses enzymes which can degrade DNA, neither the specification nor the art provide a correlation between structure and DNA destroying activity such that one of skill in the art can envision the structure of any compound that can destroy DNA. In addition, the art does not provide any teaching or guidance as to whether any fungal infection can be treated with DNase or any DNA destroying agent, or whether any DNA destroying agent can be administered to a subject without having by itself a toxic effect on the subject. As known in the art, merely finding a compound which *in vitro* or in animal models displays the desired activity for potential therapeutic use is not enough for that compound to be used directly in a subject for treatment due to (1) the potential toxic and/or unexpected effects that such compound could have on that subject, and (2) the unpredictability of observing a therapeutical effect in a subject even if a potential therapeutical effect was seen *in vitro* or in animal models. For example, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific

cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Hann et al. (Curr. Opin. Cell Biol. 13:778-784, 2001) teach that even though the mouse model is very promising for understanding human cancer, certain models are better suited for particular applications (page 778, Abstract). As taught by Hann et al., even though there are some situations where the results obtained in a mouse model mimicked those in humans, there is still not enough information to accurately predict therapeutic responses in humans using a mouse model (page 781, column 2, Therapeutic criteria).

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of testing compounds for DNA destroying activity are were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for (1) any compound (biological or chemical) for DNA destroying activity, and (2) those fungal infections that can be treated by (1). Similarly, it was not routine in the art at the time of the invention to test any number of compounds having DNA destroying activity and determine which ones can be used in a therapeutic method as claimed. In the absence of (1) a rational and predictable scheme for selecting a priori those compounds most likely to have the desired activity, (2) a correlation between structure and the ability to destroy DNA, and (3) some guidance or knowledge as to which fungal infections are more likely to be targeted by the recited agents, one of skill in the art would have to test an essentially infinite number of compounds, both chemical and biological, to determine which ones have the desired activity, which fungal infections can be treated with such compounds, and which of those compounds having DNA destroying activity can be actually used in a therapeutic method as claimed.

Therefore, taking into consideration the extremely broad scope of the claim, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and the desired function, and the high degree of unpredictability of the prior art in regard to determining which compounds are likely to have the desired activity and which of those compounds having the desired activity can be used in a therapeutic method as claimed, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Macanovic et al. (Clinical and Experimental Immunology 106:243-252, 1996). Claims 1-2 are directed in part to a method for treating diseases associated with qualitative/quantitative changes in blood extracellular DNA, wherein said method requires the administration of DNase into the systemic blood circulation. Claim 3 is directed to the method of claim 1 wherein the DNase is provided in a dose sufficient to observe a change in extracellular DNA by electrophoresis. Macanovic et al. teach a method for treatment of murine lupus, which is a disease characterized in an increase of nucleosomes in the blood due to cell apoptosis (page 244, left column, first full paragraph), by administering DNase to mice suffering from lupus via intraperitoneal injections (page 244, right column, Materials and Methods). Since Macanovic et al. teach that this treatment resulted in postponement of the development of the disease (Summary) and DNase

activity in mouse serum (Figure 1) measured by detection of DNA hydrolysis was found, the method of Macanovic et al. would be expected to reduce the levels of extracellular DNA in blood. In the absence of evidence to the contrary, one would expect this reduction in extracellular DNA would be detected by electrophoresis. Therefore, the teachings of Macanovic et al. anticipate the instant claims as written.

Conclusion

19. No claim is in condition for allowance.

20. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached at (571) 272-0811. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Primary Patent Examiner
Art Unit 1652

DR
June 23, 2009